# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 1152WOORD01 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/EP 03/13604 | 03.12.2003 | 06.12.2002 |
| International Patent Classification (IPC) or both national classification and IPC | | |
| C07D401/12 | | |
| Applicant | | |
| ALTANA PHARMA AG | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 11.06.2004 | 22.12.2004 |
| Name and mailing address of the international preliminary examining authority: | Authorized Officer |
| European Patent Office - Gitschiner Str. 103<br>D-10958 Berlin<br>Tel. +49 30 25901 - 0<br>Fax: +49 30 25901 - 840 | Hass, C<br>Telephone No. +49 30 25901-340 |

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-10 as originally filed

**Claims, Numbers**

1-20 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-19 |
| | No: | Claims | 20 |
| Inventive step (IS) | Yes: | Claims | 7-9, 16-19 |
| | No: | Claims | 1-6, 10-15, 20 |
| Industrial applicability (IA) | Yes: | Claims | 1-20 |
| | No: | Claims | - |

2. Citations and explanations

**see separate sheet**

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**V.1 Cited documents**

D1: WO 96/02535 A (COTTON HANNA KRISTINA ; LARSSON ERIK MAGNUS (SE); ASTRA AB (SE); SOERE) 1 February 1996 (1996-02-01)

D2: BONCHIO M ET AL: "The first Chiral Zirconium(IV) catalyst for highly stereoselective sulfoxidation" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 64, no. 4, 1999, pages 1326-1330, XP002242676 ISSN: 0022-3263

D3: WO 92/08716 A (BYK GULDEN LOMBERG CHEM FAB) 29 May 1992 (1992-05-29)

D4: WO 94/24867 A (SEPRACOR INC) 10 November 1994 (1994-11-10)

D5: WO 94/25028 A (SEPRACOR INC) 10 November 1994 (1994-11-10)

D6: WO 99/47514 A (KNOLL AG ; BRENNAN JAMES PATRICK (GB); TURNER ANDREW TIMOTHY (GB)) 23 September 1999 (1999-09-23)

D7: WO 96/17076 A (ASTRA AB ; HOLT ROBERT (GB); LINDBERG PER (SE); REEVE CHRISTOPHER (GB)) 6 June 1996 (1996-06-06)

**V.2 Novelty**

**V.2.1** D1 and D3 destroy the novelty of the subject-matter of claim 20; in D1, (S)-pantoprazole (the (-)-form) is even disclosed in defined enentiomeric purity. Claim 20 should thus be deleted. *Note: The formulation of claim 20 as product-by-process claim does not render the claimed product novel since normally it cannot be detected in a product how it was made. Claims for products defined in terms of processes for their preparation are admissible only if the products themselves are novel and inventive (and industrially applicable) and if there is no other information available in the application which could enable the applicant to define the product satisfactorily by reference to its composition, structure or some other testable parameter(s). In the present case, the compound can be readily defined by its chemical structure and by stereochemical parameters.*

**V.2.2** The subject-matter of claims 1-19 is novel with regard to D1 and D3 to D7 since none of these documents mentions Zr or Hf complex catalysts, and it is novel over D2 since D2 does not mention pantoprazole.

**V.3 Inventive step**

**V.3.1** According to the description, the problem underlying the present application is to provide a further process for the preparation of (S)-pantoprazole.

**V.3.2** The subject-matter of claim 20 is not novel (see above). - For claims 1-19, the closest prior art with regard to the preparation of (S)-pantoprazole is D1. This document discloses a process as defined above, comprising the sulfoxidation of an intermediate having a methylthio group to (S)-pantoprazole (which has a methylsulfinyl group), however, in D1, a titanium compound is used instead of the zirconium compound according to the present application. The following optional features, which are comprised by the present claims, are also disclosed in D1: The use of cumene hydroperoxide, the presence of an organic base (which is a tertiary amine), the use of an organic solvent optionally containing water (see D1, example 23); the organic solvent can be methyl isobutyl ketone (D1, page 15, lines 13 and 14). - Furthermore, D2 is relevant prior art as to the use of a chiral zirconium complex for stereoselective sulfoxidation. In D2, chiral zirconium complexes, especially zirconium(IV) catalysts are discussed as an alternative to titanium(IV) catalysts for stereoselective sulfoxidation reactions.

**V.3.3 Inventive step evaluation with regard to the zirconium catalyst:**

**V.3.3.1** With the knowledge of D2, the skilled person, faced with the problem defined in point V.3.1, would be encouraged to replace titanium by zirconium also in connection with the preparation of (S)-pantoprazole. So the subject-matter of claims 1 and 2 (as to the embodiment comprising the Zr complex) is to be considered, in view of the combined teachings of D1 and D2, as an obvious result from the prior art. In view of D1 and D2, claims 3 to 6 and 10 to 15 do not add subject-matter which could be regarded as non-obvious (see also point V.3.2). Consequently, claims 1 to 6 and 10 to 15 do not involve an inventive step.

**V.3.3.2** Inventive step could be acknowledged for the subject-matter of claims 7 to 9 and 16 to 19 since it could not be expected that, if Ti is replaced with Zr, a (+)-L-tartaric acid derivative instead of a (-)-L-tartaric acid derivative can be used as chiral auxiliary

reagent (the applicant submits that (+)-L-tartaric acid derivatives are easier available with respect to their more frequent natural occurrence).

**V.3.4 Inventive step evaluation with regard to the hafnium catalyst:**
Hafnium catalysts in connection with stereoselective sulfoxidation reactions are not known from any of the cited prior art documents. The use of hafnium complex catalyst in the preparation of (S)-pantoprazole is thus non-obvious for a skilled person. Therefore, with regard to the use of hafnium in the claimed process, claims 1, 3 to 5 and 7 to 15 could be considered to involve an inventive step (the remaining claims 2, 6 and 16 to 19 refer to Zr only).

**V.3.5** From the foregoing evaluation it is evident that the inventive concept providing said process by making use of a Zr complex is different from the inventive concept providing said process by making use of an Hf complex: In case of the chiral Zr complex inventive step is based on the finding that (+)-L-tartaric acid derivatives instead of (-)-L-tartaric acid derivatives can be used; in case of the chiral Hf complex inventive step is based on the fact that apparently no Hf complex hitherto has been used for sulfoxidation reactions at all. The applicant is thus informed that there is a lack of unity (within the meaning of Rule 13(1) PCT) between the subject-matter of the claims referring to Zr complexes on the one hand and subject-matter of the claims referring to Hf complexes on the other hand. However, a complete search was executed for the subject-matter of the claims, and also an international preliminary examination was carried out for the complete subject-matter of the claims on file.

**V.3.6** Claim 1 should have been restricted to such subject-matter which can be expected to actually solve the problem underlying the present application. Because of the very examples disclosed in the description it must be assumed that for carrying out the invention(s) the presence of a (+)-L-tartaric acid derivative is essential. The subject-matter of claim 7 therefore should have been introduced into claim 1 and 2 as an essential feature.

**V.4 Industrial applicability**

The subject-matter of claims 1-20 is industrially applicable.